

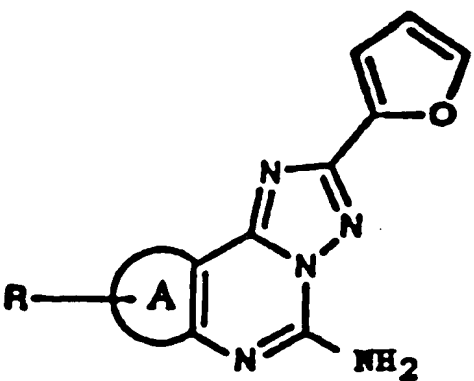
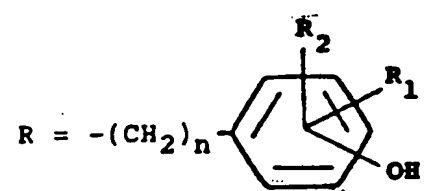
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



29/85,07  
Am

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification 6 : C07D 487/14, A61K 31/495 // (C07D 487/14, 249:00, 249:00, 239:00) (C07D 487/14, 249:00, 239:00, 231:00) (C07D 487/14, 249:00, 239:00, 235:00)</p>	<p>A1</p>	<p>(11) International Publication Number: WO 97/05138 (43) International Publication Date: 13 February 1997 (13.02.97)</p>
<p>(21) International Application Number: PCT/EP96/02881 (22) International Filing Date: 2 July 1996 (02.07.96) (30) Priority Data: MI95A001671 28 July 1995 (28.07.95) IT (71) Applicant (for all designated States except US): SCHERING-PLOUGH S.P.A. [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). (72) Inventors; and (75) Inventors/Applicants (for US only): BARALDI, Pier, Giovanni [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). CACCIARI, Barbara [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). VIZIANO, Monica [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). DIONISOTTI, Silvio [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). ONGINI, Ennio [IT/IT]; Via Ripamonti, 89, I-20141 Milano (IT). (74) Agent: MINOJA, Fabrizio; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).</p>		<p>(81) Designated States: CA, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report.</p>
<p>(54) Title: 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A<sub>2a</sub> RECEPTOR</p>		
<p>(57) Abstract</p> <p>The compounds of general formula (I), wherein A is a pyrazole, imidazole or triazole ring, R is formula (II), wherein R<sub>1</sub> and R<sub>2</sub>, which are the same or different, are H, OH, halogen, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkyl, nitro, amino, cyano, C<sub>1-4</sub> haloalkyl, C<sub>1-4</sub> haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of R<sub>1</sub> or R<sub>2</sub>, or R<sub>1</sub> and R<sub>2</sub>, can form the methylenedioxy group -O-CH<sub>2</sub>-O-; n is an integer from 0 to 4, are useful as therapeutical agents.</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(II)</p> </div>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES  
HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A<sub>2a</sub> RECEPTOR

The present invention relates to compounds having antagonistic activity on adenosine A<sub>2a</sub> receptors.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilatation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97; Williams M., Adenosine and Adenosine receptors. The Humana Press, 1990).

Adenosine action is mediated by the interaction with different membrane specific receptors which belong to the family of receptors coupled with G proteins.

Biochemical and pharmacological studies, together with the recent acquirements in the molecular biology field, have up to now allowed to identify at least 4 different adenosine receptors: A<sub>1</sub>, A<sub>2a</sub>, A<sub>2b</sub>, and A<sub>3</sub> (Pharmacol. Rev., 1994, 46, 143-156).

Intense research efforts have made it possible to identify and develop analogs to adenosine able to inte-

ract as agonists with the  $A_1$ ,  $A_{2a}$  and  $A_3$  receptors (Pharmacol. Rev., 1994, 46, 143-156).

The knowledge available on the physiological role of adenosine and its involvement in some pathological processes suggests that selective antagonists for the  $A_{2a}$  receptor can be of pharmacological interest. At the level of the central nervous system, antagonistic  $A_{2a}$  compounds could have antidepressive properties and stimulate the cognitive functions. Moreover, numerous data show that the  $A_{2a}$  receptors are present in high density in the basal ganglia of which the importance in the control of movement is known. Hence, the hypothesis that  $A_{2a}$  antagonists can improve motor-impairment due to neurodegenerative processes. Amongst these are included Parkinson's disease, senile dementia as in Alzheimer's disease and psychosis of organic origin (Drug Dev. Res., 1993, 28, 381-385).

At a peripheral level,  $A_{2a}$  receptor antagonists could stimulate the respiratory functions and therefore have a therapeutic effect in the treatment of broncho-spasm and, more generally, asthma. Moreover, with regard to the effects at a cardiovascular or renal level, an advantageous activity on renal flow can be envisaged and therefore the possibility of the treatment of renal insufficiency and of various cardiovascular disturbances.

Whilst some xanthine-structure have been known to be  $A_1$  receptor selective antagonists (J Med. Chem., 1992, 35, 407-422), only recently novel xanthine (J. Med. Chem, 1993, 36, 3731-3733) and non-xanthine (PCT WO 9501356, published on 12 01.95, corresponding to Italian

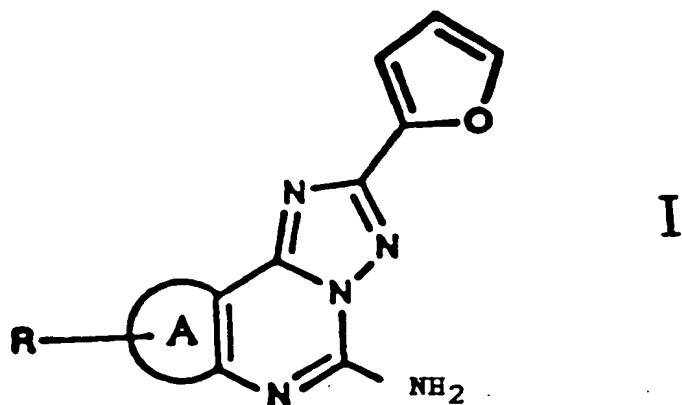
3

Patent application MI93A001396) Bioorg. Med. Chem. Lett, 1994, 4, 2539-2544) have been found to have high A<sub>2a</sub> affinity and moderate A<sub>2a</sub> vs A<sub>1</sub> selectivity (about 50-fold).

5 The compounds disclosed in WO 9501356 are 1,2,4-triazolo[1,5-c]pyrimidine heterocyclic analogues, on the heterocyclic ring of which is present, inter alia, an aryl group, particularly phenyl or phenylalkyl, optionally substituted with halogen atoms, C<sub>1</sub>-C<sub>4</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkyl, nitro, amino, cyano, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>1</sub>-C<sub>4</sub> haloalkoxy, carboxy, carboxamido groups.

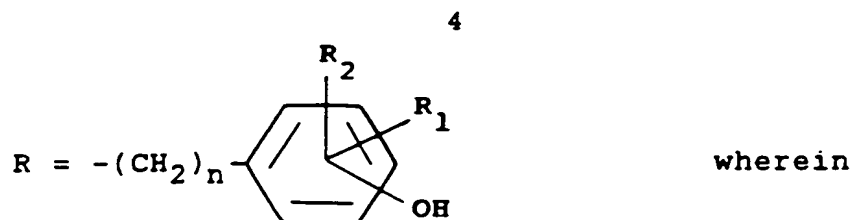
Moreover, it has surprisingly been found that the presence of at least one hydroxyl on the phenyl ring gives the compounds disclosed in WO9501356 an increased A<sub>2a</sub> selectivity.

Therefore, the present invention relates to compounds of general formula I:



30 wherein:

A is a pyrazole, imidazole or triazole ring



5  $\text{R}_1$  and  $\text{R}_2$ , which are the same or different, are H, OH, halogen,  $\text{C}_1$ - $\text{C}_4$  alkoxy,  $\text{C}_1$ - $\text{C}_4$  alkyl, nitro, amino, cyano,  $\text{C}_1$ - $\text{C}_4$  haloalkyl,  $\text{C}_1$ - $\text{C}_4$  haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of  $\text{R}_1$  or  $\text{R}_2$ , or  $\text{R}_1$  and  $\text{R}_2$ , can form the methylenedioxy group

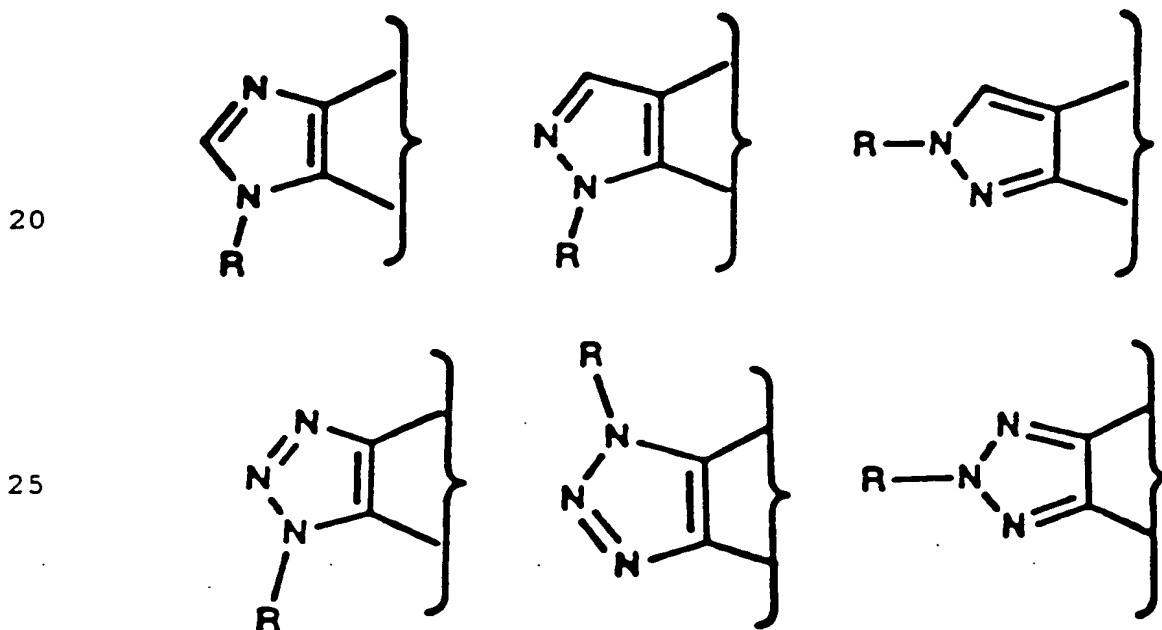
10  $-\text{O}-\text{CH}_2-\text{O}-$ ;

$n$  is an integer from 0 to 4.

The invention also comprises the pharmaceutically acceptable salts of the compounds of general formula I.

The possible meanings of A can be represented by

15 the following structural formulae:



30 Examples of  $\text{C}_1$ - $\text{C}_4$  alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and isobutyl.

Examples of  $\text{C}_1$ - $\text{C}_4$  alkoxy groups are methoxy,

5

ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy.

Halogen atoms are fluorine, chlorine, bromine, iodine.

5 Examples of  $C_1-C_4$  groups haloalkyl are trifluoromethyl, 2-fluoroethyl, 2-chloroethyl.

Examples of  $C_1-C_4$  haloalkoxy groups are trifluoromethoxy chloromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy.

10 Preferred compounds of formula I are those wherein A is pyrazolo[4,3-e] or 1,2,3-triazolo[5,4-e].

Particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n ranges from 1 to 4 included, preferably 2 or 3, the OH group on the phenyl ring is at the para position and  $R_1$  and  $R_2$  are hydrogen.

15 A second group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 3, preferably 1 or 2, the OH group on the phenyl ring is at the meta position and  $R_1$  and  $R_2$  are hydrogen.

20 A third group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position,  $R_1$  is methoxy, preferably at the meta position,  $R_2$  is hydrogen.

25 A fourth group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position,  $R_1$  is hydroxy, preferably at the meta position,  $R_2$  is hydrogen.

30 A fifth group of particularly preferred compounds of formula I are those wherein A is 1,2,3-triazolo[5,4-

e], n is from 1 to 4, preferably 2 or 3, and the OH group on the phenyl ring can be at all the possible positions.

Particularly preferred are the following compounds:

- 5 5-amino-7- $[\beta$ -(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7- $[\beta$ -(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7- $[\beta$ -(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
10 5-amino-7- $[\gamma$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
15 5-amino-7- $[\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-8- $[\beta$ -(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-8- $[\gamma$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
20 5-amino-8- $[\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-8- $[\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
25 5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7- $[\beta$ -(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7- $[\beta$ -(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
30

7

- 5-amino-7- $\{\chi$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-  
1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7- $\{\chi$ -(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-  
furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]py-  
5 rimidine;  
5-amino-7- $\{\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-  
1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7- $\{\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-  
furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-  
10 pyrimidine;  
5-amino-8- $\{\beta$ -(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-  
triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-8- $\{\chi$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-  
1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
15 5-amino-8- $\{\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-  
1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-8- $\{\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-  
furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-  
pyrimidine;  
20 5-amino-7- $\{\beta$ -(4-hydroxy-3-iodo)-phenylethyl]-2-(2-  
furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7- $\{\chi$ -(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-  
furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7- $\{\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-  
25 furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

The compounds according to the present invention are prepared with known processes, in particular they are according to the processes described in WO Application 9501356.

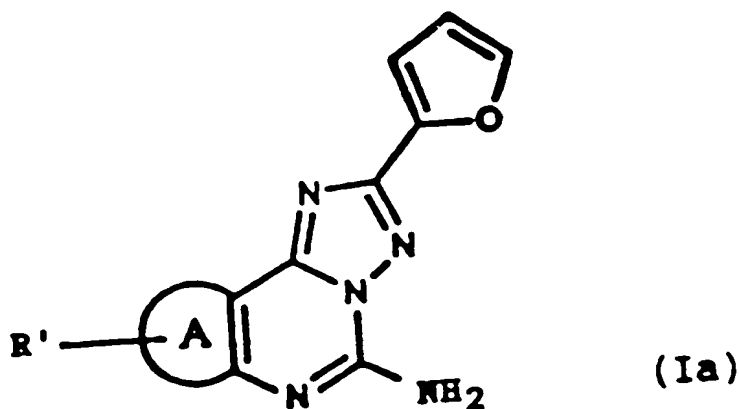
- 30 As in all the compounds of formula I at least one OH group is present on the phenyl ring, it is necessary

8

to protect the OH group(s), during the various synthetic steps. The final compounds of formula I are thus obtained by deprotecting the phenyl OH group(s) once the complete structure has been obtained. Protection methods are conventionally known, for example as described in T. W. Greene, P.G.M. Woots, Protective Groups in Organic Synthesis, J. Wiley. N.Y. 1991, 2nd Edition.

A preferred protection method is the benzylation and following debenylation on Pd/C in tetrahydrofuran. Alternatively, the protection method involves the use of the allyl group or, when two adjacent hydroxy groups are present, the methylenedioxy group.

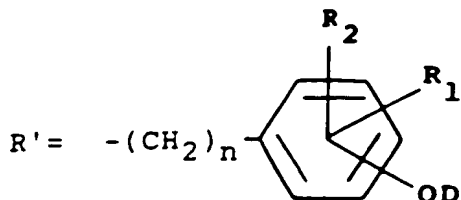
Therefore, another object of the present invention is a process for the preparation of compounds of formula (I), as reported above, which comprises the deprotection of the phenyl hydroxy groups of the compounds of formula (Ia)



wherein:

9

A is as defined in formula (I);



10 wherein D is a suitable protective group, preferably benzyl or allyl (or  $-CH_2-$  as protective group of two adjacent hydroxyl groups),  $R_1$  and  $R_2$ , which are the same or different, are hydrogen, OD, wherein D is as defined above, a halogen atom,  $C_1-C_4$  alkyl, nitro, amino, cyano,  $C_1-C_4$  halogen alkoxy, carboxy, carboxamido group; n is as above defined.

15 The process according to the present invention also comprises the optional transformation of the obtained compound into a pharmaceutically acceptable salt.

#### BIOLOGICAL ACTIVITY

The pharmacological properties of the disclosed compounds were studied in the most sensitive and suitable experimental models both *in vitro* and *in vivo*.

20 The compounds of general formula I have advantageous properties of selectivity for the  $A_{2a}$  receptor compared with those described in the above cited WO 9501356.

25 Adenosine  $A_{2a}$  receptor affinity was tested by means of receptor binding techniques on bovine and rat (Sprague-Dawley strain), cerebellar corpus striatum, which is a tissue rich in  $A_{2a}$  receptors. Compound  $^3H$ -CGS 21680 (J. Pharm. Exp. Ther. 1989, 251, 888-893) was used as the radioligand. The  $A_1$  receptor affinity was tested  
30 with receptor binding techniques on bovine and rat (Sprague-Dawley strain), cerebellar cortex membranes,

10

which is a tissue rich in  $A_1$  receptors.  $^3H$ -Cyclohexyl-adenosine,  $^3H$ -CHA (Proc. Natl. Acad. Sci. - USA - 1980, 77, 5547-5551) was used as the radioligand. The selectivity for the  $A_{2a}$  receptor was evaluated from the comparison between the affinities for the  $A_1$  or  $A_{2a}$  receptor shown by each compound. A number of experimental data support the evidence that a marked relationship exists between the affinity found with binding techniques in brain tissues and the physiological effects modulated by adenosine receptors.

$A_{2a}$  receptors are mainly present in the vascular system and the stimulation thereof causes vasodilation. Therefore, the  $A_{2a}$  antagonistic activity of these molecules has been studied by evaluating the capability of inhibiting vasodilation induced by adenosine agonists in vascular tissues such as rat aorta and bovine or porcine coronary arteries.

These compounds were unable to antagonize negative chronotropic effects induced by  $A_1$  receptor agonists when tested on isolated rat atria (Br. J. Pharmacol., 1983, 78, 207-212).

Another test to evaluate the antagonistic activity of the new compounds is the study of platelet aggregation. In fact, adenosine or the analogues thereof are known to inhibit platelet aggregation induced by different aggregatory agents, among which ADP. Therefore, the capability of the novel compounds of antagonizing the inhibitory effect induced by NECA or CGS 21680 agonists was tested using rabbit platelets.

This test is particularly important as only the  $A_{2a}$  receptor is present on platelet cell membranes.

The in vivo activity was evaluated in Swiss mice and spontaneously hypertensive rats (SHR). The behavioural response to a treatment with different doses of the tested compounds administered parenterally was evaluated in the mice. In the SHR rats, the tested compounds were administered parenterally at increasing doses and the capability thereof of antagonizing the bradycardic and hypotensive effects induced by A<sub>1</sub> and A<sub>2a</sub> receptor agonists, respectively, was measured.

A number of the compounds of formula I showed a marked A<sub>2a</sub> affinity with K<sub>i</sub> ranging from 1 to 10 nM. The A<sub>2a</sub> selectivity for some compounds is 200-800fold, which is markedly higher than that of the compounds known up to now.

In the platelet aggregation test, said compounds proved to effectively block the antiaggregatory effects induced by A<sub>2a</sub> agonists, with pA<sub>2</sub> values ranging from 8 to 10.

The compounds of the invention antagonize in a variety of vascular districts, with a similar potency, vasodilatation mediated by A<sub>2a</sub> receptors, whereas they are not able of blocking the negative chronotropic effect induced by A<sub>1</sub> agonists in rat isolated atria. In the in vivo models, the tested compounds showed a poor stimulating activity on central nervous system, they antagonized the hypotension induced by A<sub>2a</sub> agonists without changing significantly the heart rate. The compounds turned out to be active at doses from 0.001 to 3 mg/kg intraperitoneally.

For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical composi-

12

tions, which can be administered, for example, by the oral, parenteral or transdermal routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, XVII ed. Said compositions are comprised within the scope of the present invention.

The daily dosage will depend, of course, on many factors (severity of the pathology to treat, patient conditions, toxicology and pharmacokinetic of the selected compound) but generally it will range from 0.01 to 10 mg/kg body weight, preferably from 0.1 to 1 mg/kg, optionally subdivided in more administrations. Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms, transdermal forms (patches) and the like.

The following examples further illustrate the invention.

#### Example 1

5-amino-7-[ $\beta$ -(4-hydroxy)-phenylethyl]-2-(furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine.

A solution of 5-amino-7-[ $\beta$ -(4-benzyloxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine (1.5 g; 0.003 moles) in THF (20 ml) is added with  $\text{HCOONH}_4$  (0.81 g, 0.012 moles) and 10% C-Pd (0.3 g) and refluxed for 2 hours. When the reaction is complete, the catalyst is filtered off and the supernatant is concentrated. The residue is chromatographed (AcOEt) to give 0.44 (41%) of the desired compound, which is a white solid, m.p. 265 (dec.). IR (KBr)  $\text{cm}^{-1}$ : 3500-3100. 1650. 1610. 1525, 1435;  $^1\text{H}$  NMR (DMSO)  $\delta$ : 3.04, (t, 2H,  $J=8$  Hz); 4.41 (t,

13

2H, J=8 Hz); 6.60 (d, 2H, J=8 Hz); 6.73-6.74 (m, 1H);  
6.93 (d, 2H, J=8); 7.22 (d, 1H, J=4 Hz); 7.94 (s, 1H);  
8.07 (bs, 2H); 8.16 (s, 1H), 9.22 (s, 1H).

### Example 2

5        0.25 ml of an 1M BCl<sub>3</sub> solution in CH<sub>2</sub>Cl<sub>2</sub> were added  
at 0°C to a solution of 50 mg (0.12 mmol) of 5-amino-7-  
[β-(3,4-methylenedioxy)phenylethyl]-2-(2-furyl)-pyrazo-  
le-[4,3-e]-1,2,4-triazole-[1,5-c]-pyrimidine.

10        The mixture was left at 4°C for 5 h. 1 ml of  
methanol was added and the solvent was evaporated, to  
give 33 mg of the corresponding 3,4-dihydroxy derivative  
(m.p. 272° dec.).

### Example 3

15        Following the same procedures of Example 1 or 2,  
starting from the suitable benzyloxy- or methylenedioxy-  
substituted precursors, the following compounds were  
obtained:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-fu-  
ryl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
20        5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyra-  
zolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyra-  
zolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7-[χ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-  
25        pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine;  
m.p. 189-191°C;  
5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-  
1,2,4-triazolo[1,5-c]pyrimidine, m.p. > 280°C;  
5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-  
30        pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-8-[χ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-

- pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-8-[ $\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-  
pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-8-[ $\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-  
5 furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-  
1,2,4-triazolo[1,5-c]pyrimidine;  
5-amino-7-[ $\beta$ -(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-  
triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
10 5-amino-7-[ $\beta$ -(4-hydroxy-3-iodo)-phenylethyl]-2-(2-  
furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-  
pyrimidine;  
5-amino-7-[ $\gamma$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-  
1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
15 5-amino-7-[ $\gamma$ -(3,4-dihydroxy)-phenylpropyl]-2-(2-furyl)-  
1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
m.p. 204-206°C;  
5-amino-7-[ $\gamma$ -(3,4-methylenedioxy)-phenylpropyl]-2-(2-  
furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-  
20 pyrimidine; m.p. 210-211°C;  
5-amino-7-[ $\gamma$ -(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-  
furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyri-  
midine;  
5-amino-7-[ $\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-  
25 1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-  
furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-  
pyrimidine;  
5-amino-8-[ $\beta$ -(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-  
30 triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-8-[ $\gamma$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-

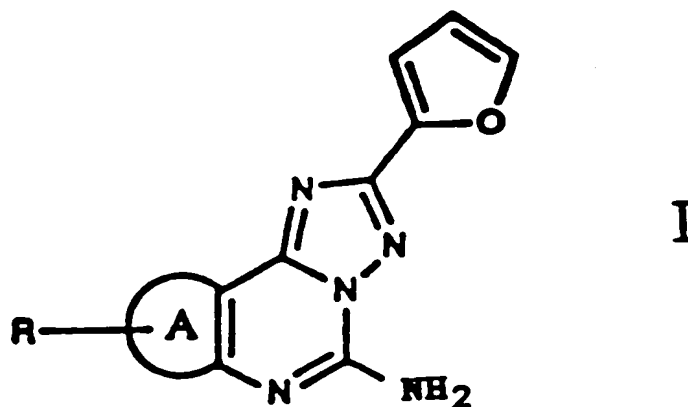
15

- 1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-8-[ $\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-  
1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-8-[ $\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-  
5 furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-  
pyrimidine;  
5-amino-7-[ $\beta$ -(4-hydroxy-3-iodo)-phenylethyl]-2-(2-  
furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\gamma$ -(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-  
10 furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-  
furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine.

16

CLAIMS

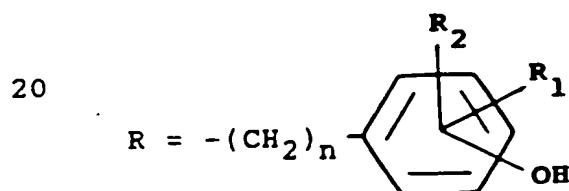
1. Compounds of general formula (I)



15

wherein:

A is a pyrazole, imidazole or triazole ring



wherein

25  $R_1$  and  $R_2$ , which are the same or different, are H, OH, halogen,  $C_1$ - $C_4$  alkoxy,  $C_1$ - $C_4$  alkyl, nitro, amino, cyano,  $C_1$ - $C_4$  haloalkyl,  $C_1$ - $C_4$  haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of  $R_1$  or  $R_2$ , or  $R_1$  and  $R_2$ , can form the methylenedioxy group  $-O-CH_2-O-$ ;

$n$  is an integer from 0 to 4,

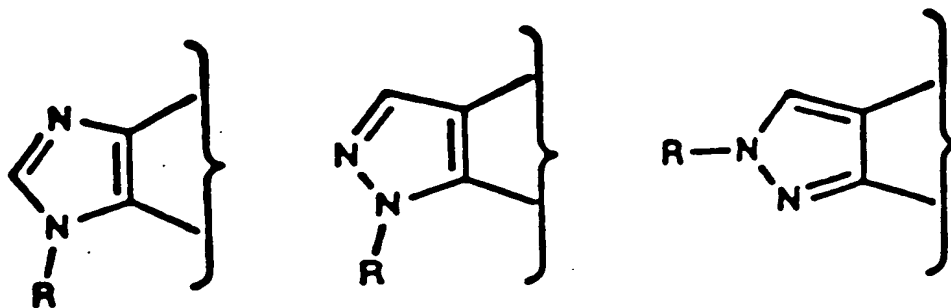
30 and the pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein A is a

17

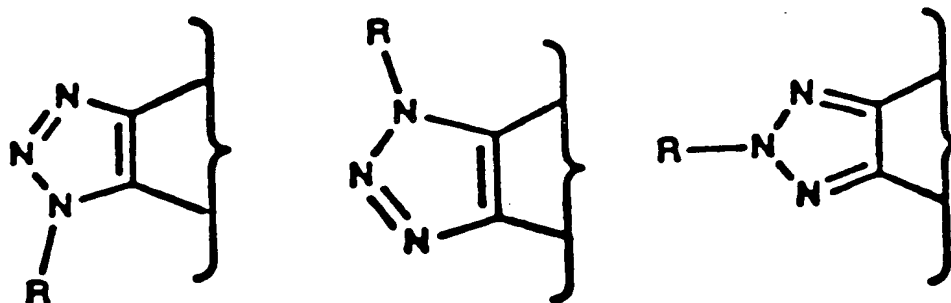
group selected from

5



10

15



3. Compounds according to claim 1, wherein A is  
 20 pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3,  
 the OH group on the phenyl ring is at the para position  
 and R<sub>1</sub> and R<sub>2</sub> are hydrogen.

4. Compounds according to claim 1, wherein A is  
 25 pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3,  
 the OH group on the phenyl ring is at the meta position  
 and R<sub>1</sub> and R<sub>2</sub> are hydrogen.

5. Compounds according to claim 1, wherein A is  
 pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3,  
 the OH group on the phenyl ring is at the para position,  
 30 R<sub>1</sub> is methoxy, preferably at the meta position, R<sub>2</sub> is  
 hydrogen.

18

6. Compounds according to claim 1, wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position, R<sub>1</sub> is hydroxy, preferably at the meta position, R<sub>2</sub> is hydrogen.

7. Compounds according to claim 1, wherein A is 1,2,3-triazolo[5,4-e], n is from 1 to 4, preferably 2 or 3, and the OH group on the phenyl ring can be at all the possible positions.

8. A compound according to claim 1, selected from the group consisting of:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

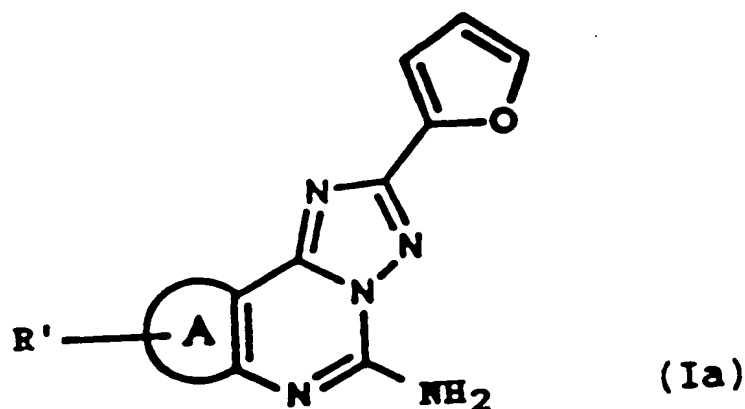
5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

- 5-amino-7-[ $\beta$ -(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\beta$ -(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\gamma$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\gamma$ -(3,4-dihydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
10 5-amino-7-[ $\gamma$ -(3,4-methylenedioxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\gamma$ -(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
15 5-amino-7-[ $\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-7-[ $\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
20 5-amino-8-[ $\beta$ -(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-8-[ $\gamma$ -(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
25 5-amino-8-[ $\beta$ -(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
5-amino-8-[ $\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
30 5-amino-7-[ $\beta$ -(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

20

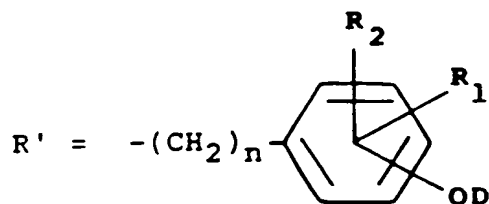
5-amino-7-[ $\gamma$ -(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;  
 5-amino-7-[ $\beta$ -(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine.

9. A process for the preparation of the compounds of claims 1 to 8, which comprises the deprotection of the phenyl hydroxy groups of the compounds of formula (Ia)



wherein:

- A is as defined in formula (I);



- wherein D is a suitable protective group, preferably benzyl or allyl,

- $R_1$  and  $R_2$ , which are the same or different, are hydrogen, OD, wherein D is as defined above, a halogen atom,  $C_1$ - $C_4$  alkyl, nitro, amino, cyano,  $C_1$ - $C_4$  halogen alkoxy, carboxy, carboxamido groups; n is as defined above.

21

10. A process according to claim 9, wherein D is benzyl and the deprotection is performed with Pd/C in tetrahydrofuran.

5 11. A process according to claim 9, wherein the methylenedioxy group is deprotected to dihydroxy derivative.

12. Pharmaceutical compositions containing as the active ingredient a therapeutically effective amount of a compound of the claims 1-8 in admixture with  
10 conventional carriers and excipients.

**This Page Blank (uspto)**

# INTERNATIONAL SEARCH REPORT

Int. Application No  
PCT/EP 96/02881

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07D487/14 A61K31/495 //(C07D487/14,249:00,249:00,239:00),  
(C07D487/14,249:00,239:00,231:00),(C07D487/14,249:00,239:00,  
235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 01356 (SCHERING PLOUGH S P A ;BARALDI PIER GIOVANNI (IT); ZAPPATERRA LAUR) 12 January 1995 cited in the application see claim 1 -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \* & \* document member of the same patent family

Date of the actual completion of the international search

16 October 1996

Date of mailing of the international search report

25.10.96

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL- 2280.HV Rijswijk  
Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl,  
Fax ( + 31-70) 340-3016

Authorized officer

De Jong, B

### Information on patent family members

PCT/EP 96/02881

Form PCT ISA 210 (patent family annex) (July 1992)